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Supplementary Material

3D-QSAR and Molecular Docking Approaches for the Identification of Novel Phyto-inhibitors of the Cyclin-dependent Kinase 4

Damilohun Samuel Metibemu

Department of Biochemistry, Adekunle Ajasin University, Akungba-Akoko, Ondo State, Nigeria

Table S1 The glide scores of the phytochemicals of *Argerantum conyzoides*, *Cannabis sativa* and *Zingiber offinale* docked into the cyclin-dependent kinase 4 (CDK4) catalytic site.

Phytochemicals of *Argerantum conyzoides*	**Glide scores**	**Phytochemicals of *Cannabis sativa***	**Glide scores**	**Phytochemicals of *Zingiber officinale***	**Glide scores**
Kaempferol-3,7-O -Diglucoside	-7.247	Catechin	-7.811	Nicotinic Acid	-6.181
Quercetin	-7.137	Isovitexin	-7.364	Dehydrozingerone	-5.786
Kaempferol	-7.039	Grossamide	-7.247	Riboflavin	-5.74
Sesamin	-6.218	Quercetin	-7.137	12-Shogaol	-5.733
Conyzorigum	-5.701	Kaempferol	-7.039	Vitamin C	-5.465
2H Chromene	-5.632	Secoisolariciresinol	-6.613	Zingerone	-5.465
2 Methoxyflavone	-5.631	Naringenin	-6.591	Galanal B	-5.43
Nobiletin	-5.62	Luteolin -7-o Glucoside	-6.374	10-Gingerol	-5.332
Chromones	-5.464	Epicatechin	-6.353	Galanal A	-5.317
Prococene 2	-5.338	Cephradine	-6.165	Vitamin A	-5.303
7 Methoxy	-5.314	Chrysin	-5.945	Thiamine	-5.293
Precocene 1	-5.314	Lacriresinol	-5.805	Phenol	-5.098
4 Methoxyflavone	-5.314	Cannflavinb	-5.767	Yakuchinone-A	-4.971
5 Methoxyflavone	-5.19	Serpyllin	-5.698	8-Paradol	-4.919
6 Methoxyflavone	-5.181	Sophoroside	-5.573	Sequiterpene	-4.74
Aurantiamide Acetate	-5.14	Cannabielsoin	-5.544	Beta-Phellandrene	-4.662
Phenol	-5.098	Guaiol	-5.5	Alpha Phellandrene	-4.572
3 Methoxyflavone	-5.032	Pinoresinol	-5.461	1-Dehydro-10-Gingerdione	-4.552
Caffeic Acid	-4.983	Dihydroresveratrol	-5.426	Borneol	-4.516
Coumarin	-4.981	Medioresinol	-5.289	Bisabolene	-4.48
7 Methoxyflavone	-4.79	Cephradine	-5.27	6 Gingersulfonic Acid	-4.442
Beta Cubebene	-4.764	Malvidin	-5.252	Galanolactone	-4.382
Ethyl Vanillin	-4.76	Cannabitriol	-5.161	Gelanolactone	-4.382
Gamma Cardinene	-4.65	Cannabichromene	-5.148	Zerumbone	-4.369
Flavone	-4.619	Luteolin	-5.122		
Trans Cinnamic Acid	-3.317	Baicalein	-5.016		
		Terpinolene	-4.9		
		Ergosterol	-4.835		

Table S2 The glide scores of the phytochemicals of *Graviola*, *Occimum gratissimum* and *Tinospora cordifolia* docked into the cyclin-dependent kinase 4 (CDK4) catalytic site.

Phytochemicals of Graviola	**Glide score**	**Phytochemicals of *Oscimum gratissimum***	**Glide score**	**Phytochemicals of *Tinospora cordifolia***	**Glide score**
Annohexocin	-7.58	Isovitexin	-7.364	(-)Litcubinine	-8.081
Coclaurine	-6.962	Nepetoidin A	-6.303	Aporphine	-6.846
Casuarine	-6.869	Hymenoxin	-5.484	(-) Epicatechin	-6.39
Coreximine	-6.579	Sinapic Acid	-5.452	Syringin	-6.165
Annopentocin A	-6.538	Ethyl Cinnamate	-5.419	N Formylannonaine	-6.144
Stepharine	-6.419	Trans Sabiene Hydrate	-5.321	Berberine	-5.919
N-Methylcoclaurine	-6.406	Rosmarinic Acid	-5.274	Isocolumbin	-5.893
(+)-Isoboldine	-6.356	Gamma-Eudesmol	-5.208	Salsolinol	-5.887
Isolaureline	-6.131	Nevadensin	-5.199	Bergenin	-5.872
Ijms Annonaine	-6.019	Salvigenin	-5.167	Palmatosidec	-5.783
Reticuline	-5.914	Luteolin	-5.122	Palmatosidec	-5.699
Xylopine	-5.838	Apigenin 7,4'-Dimethyl Ether	-5.044	Diosmetin	-5.439
Liriodenine	-5.829	Xanthomicrol	-5.006	Tembetarine	-5.415
Swainsonine	-5.771	Terpinolene	-4.9	Cordifolisidec	-5.317
Anomuricine	-5.737	Thymol	-4.892	Tetrahydropalmatime	-5.308
Donhexocin	-5.708	Fenchone	-4.809	D Glucopyranoside	-5.298
Annopentocin B	-5.692	Apigenin	-4.77	Jatorrhizine	-5.268
Annonacin A	-5.655	P-Cymene	-4.667	Jatrorrhizine	-5.262
Annonacin	-5.61	1,8-Cineole	-4.665	Morphine	-5.218
Asimilobine	-5.563	Methyl Isoeugeneol	-4.614	Epoxyclerodane	-5.218
IJMS Asimilobine	-5.563	T-Cadinol	-4.605	Palmatine	-5.102
Annocatalin	-5.457	Alpha-Copaene,	-4.498	Cordioside	-5.091
Remerine	-5.385	Bisaboline	-4.48	Ecdysterone	-5.062
Corossolin	-5.342	Camphor	-4.375	Thymol	-4.994
Anomurine	-5.326			Lysicamine	-4.892
Casuarine	-5.301			20betaecdysone	-4.824
Annopentocin C	-5.293			Apigenin	-4.802
Annonamine	-5.248			(-)Litcubinine	-4.798
Khellin Coronin	-5.232			Palmatosideg	-4.77
Javoricin	-5.154			Tinocordifolin	-4.486
Annomontacin	-5.027			Tyramine	-4.41
Deoxymannojirimycin	-4.985			Magnoflorine	-4.372
Nornuciferine	-4.974			Tetrahydrofuran	-4.279
Annoglaxin	-4.97			Phenylpropene	-4.274
Annoreticuin-9-One	-4.912			Makisteronea	-4.26
Cis-Corossolone	-4.71				
Muricapentocin	-4.621				
Atherosperminine	-4.572				
Annomuricin E	-4.559				
Dnj	-4.514				
Gigantetronenin	-4.504				

Table S3 Glide score of the lead phyto-compounds and the standard drug, Palbociclib.

Phytochemicals	Glide scores
catechin	-7.811
kaemferol	-7.247
Quercetin	-7.126
Coclaurine	-6.94
secoisolariciresinol	-6.612
Narigenin	-6.586
Coreximine	-6.524
Stepharine	-6.402
N-methylcoclaurine	-6.369
aporphine	-6.351
(+)-Isoboldine	-6.289
Nepetoidin A	-6.18
nicotinic acid	-6.171
epicatechin	-6.165
Isolaureline	-6.093
Palbociclib	-5.78

Table S4 Validation of glide scores.

Correlations						
					pChemblValue	Glidescore
Spearman's rho	pChemblValue	Correlation Coefficient			1.000	.829**
		Sig. (2-tailed)				.000
		N			108	108
		Bootstrap[b]	Bias		0.000	-.005
			Std. Error		0.000	.029
			BCa 95% Confidence Interval	Lower		.777
				Upper		.869

** Significant positive correlation at $p<0.01$ level

Table S5 The drug-likeness using the Lipinski Rule of Five.

Hit compounds	Plants	H.B.A (<=10)	H.B.D (<=5)	nR.B (<=10)	XLog P (<=5)	M.M (<500)	P.S.A (<140)
Kaemferol	Argerantum	6	4	1	1.9	286.239	107
Quercetin	Argerantum	7	5	1	1.5	302.238	127
Catechin	Cannabis	6	5	1	0.4	290.71	110
Narigenin	Cannabis	2	4	1	2.4	272.257	100.803
Secoisolariciresinol*	Cannabis	4	6.4	9	2.5	362.422	104.256
Epicatechin*	Cannabis	5	5.45	1	0.4	290.272	115.679
nicotinic acid	Ginger	1	3.5	1	0.4	123.111	62.541
(+)-Isoboldine	Graviola	2	5	2	2.2	327.379	62.061
Coclaurine	Graviola	3	3.75	3	2.6	285.342	67.156
Coreximine	Graviola	2	5	2	2.6	327.379	64.986
Isolaureline	Graviola	0	4.25	1	3.3	309.364	30.077
N-methylcoclaurine	Graviola	2	4.25	3	3	299.369	56.47
Stepharine	Graviola	1	5	2	2.1	297.353	59.575
Nepetoidin A*	Oscimum	4	5.5	5	2.7	314.294	123.686
Aporphine	Tinospora	0	2	0	3	235.328	5.46
Palbociclib$		8	2	5	1.8	447.543	103

Note: P.S.A = Polar Surface Area
H.B.A = Hydrogen Bond Acceptor
H.B.D= Hydrogen Bond Donor
R.B = Rotatable Bonds
M.W = Molecular Weight
* = Compounds that violate one rule of Lipinski
$= Standard drugs

Table S6 The pIC_{50} of the observed and predicted values from some of the compounds in the training set.

Chembl_ID	Observed pIC_{50}	Predicted pIC50	Residual
CHEMBL213805	5.2200	4.96228	.00136
CHEMBL457179	4.5900	4.64163	-.00235
CHEMBL456796	4.4800	4.53912	-.00818
CHEMBL458075	4.9600	4.90479	-.01186
CHEMBL456143	4.6200	4.55148	-.01452
CHEMBL456995	4.9200	5.04587	.00002
CHEMBL525921	4.6200	4.58225	-.01028
CHEMBL456965	4.1000	4.04854	-.00656
CHEMBL515051	4.5200	4.44587	-.00580
CHEMBL457190	4.7200	4.39153	.00799
CHEMBL456760	4.5900	4.51261	-.0578
CHEMBL498521	4.9500	5.09991	-.0354
CHEMBL463384	4.6000	4.70700	-.00221
CHEMBL457401	4.6400	4.56495	-.03454
CHEMBL463383	5.0500	4.95302	-.00097
CHEMBL458076	4.1300	4.37230	.00170
CHEMBL521733	4.8000	4.77291	.00677
CHEMBL527039	4.3200	4.28754	.01349
CHEMBL496481	4.8200	4.70924	.00828
CHEMBL525530	4.4200	4.41114	.00191
CHEMBL525538	4.3100	4.37005	.00277
CHEMBL498130	4.0700	4.52704	-.00478
CHEMBL497454	4.4200	4.48498	-.00891
CHEMBL515674	4.4600	4.51642	-.01795
CHEMBL498710	5.0400	4.90014	.00137
CHEMBL456584	4.7700	4.75157	.03758
CHEMBL456113	4.6600	4.73511	.01620
CHEMBL258765	6.2600	6.23751	-.00815
CHEMBL455931	4.7500	4.90295	.02947
CHEMBL517154	4.5000	4.38026	.01747